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Syndrome of Microcephaly, Facial and Hand Abnormalities, Tracheoesophageal Fistula, Duodenal Atresia, and Developmental Delay

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We report on six new families (12 new patients) with the syndrome of microcephaly, facial and hand abnormalities, tracheoesophageal fistula, duodenal atresia, and developmental delay. The most common findings were hand abnormalities, microcephaly, short and/or narrow palpebral fissures, broad nasal bridge, anteverted nostrils, ear abnormalities, and micrognathia. Inheritance is autosomal dominant. There is a significant amount of intrafamilial variability especially as it relates to the gastrointestinal findings. Although the first patients reported, who were very young, did not exhibit any developmental delay, they subsequently did develop learning problems, and 87% of our 12 patients had mental retardation or learning difficulties. Am. J. Med. Genet. 69:245–249, 1997.

KEY WORDS: microcephaly; dysmorphic facies; hand abnormalities; tracheoesophageal fistula; duodenal atresia; developmental delay

INTRODUCTION

In 1975, we reported on a father, son, and grandmother with microcephaly, hand abnormalities, tracheoesophageal fistula, duodenal atresia, and normal intelligence [Feingold, 1975]. In 1978, we reported a mother and daughter with similar findings except for the absence of tracheoesophageal fistula and duodenal atresia, [Feingold, 1978]. König et al. [1990] described a mother and son and Brunner and Winter [1991] reported two other families with findings similar to the patients described by Feingold.

We report on six new families (12 new patients) with this syndrome, update the findings of the original families, and more clearly define the syndrome.

CLINICAL REPORTS

Family 1

A 2-year-old girl (Patient 1) was referred to Children's Hospital in New Orleans for microcephaly, mild developmental delay, and abnormal facial findings. Pregnancy was uneventful and there was no history of exposure to infectious agents, radiation, drugs, or known teratogens. Spontaneous vaginal delivery took place at 35 weeks of gestation and birth weight was 2,115 g. At birth a tracheoesophageal fistula was present and was repaired at age 2 days. No other abnormalities were described at that time. Microcephaly was noted at age 1¼ years. At age 2 her development was 5–6 months behind the normal range.

On physical examination her length was 88.4 cm (35th centile), weight 10.4 kg (5th centile), and head circumference (OFC) 44.2 cm (50th centile for a 9-month-old. She had epicanthal folds, blue sclerae, small palpebral fissures, posteriorly angulated ears, flat tip of the nose, anteverted nostrils, prominent lips, slight micrognathia, (Fig. 1) mild syndactyly of the third and fourth fingers, disruption of normal palmar creases, extra finger flexion creases of the middle phalanx of the third and fourth fingers of the right hand, and hyperextensibility of the left thumb. Other physical findings included a transverse umbilical hernia, patent ductus arteriosus, and the second toe overriding the first and third toes. Chromosomes were normal. Bone age was mildly delayed.

Her mother (Patient 2) was developmentally delayed and attended special classes for 2 years, but did graduate from high school. On physical examination the mother's phenotype was very similar to her daughter's. Head circumference was 47.8 cm, 50th centile for a 20-month-old. Her face was triangular with slight

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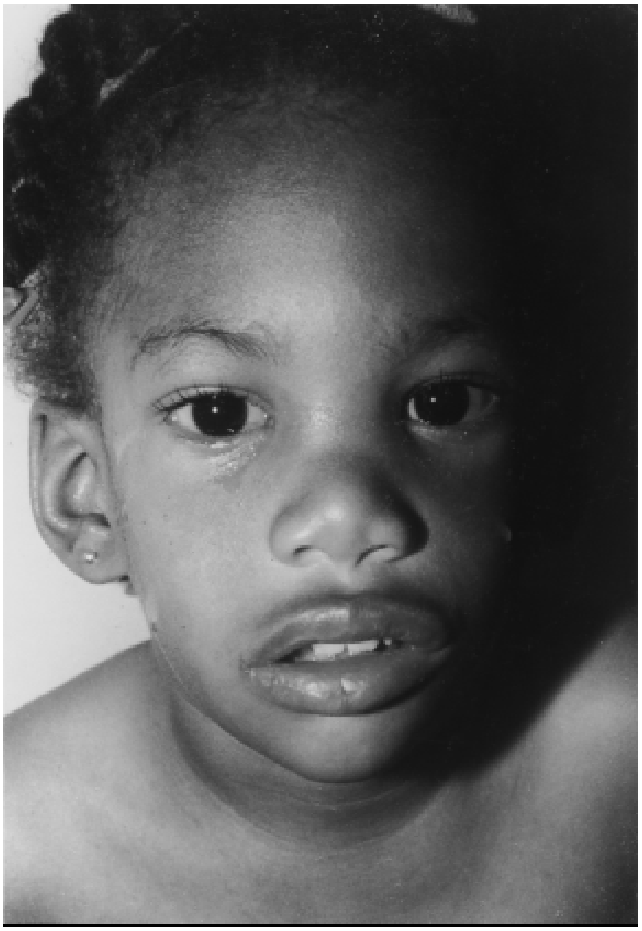

Fig. 1. Face of patient 1 showing epicanthal folds, small palpebral fissures, posteriorly angulated ears, flat tip of the nose, prominent lips, and micrognathia.

upslanting of palpebral fissures, prominent eyes and lips, high-arched palate, micrognathia, and asymmetry of her face (Fig. 2). Her hands were similar to those of her daughter, and she was unable to flex the distal phalanx of the right thumb. On X-ray examination, fusion of the lunate and triquetrum was present.

The mother's younger brother, who was not examined, was deaf and had congenital heart disease. His photographs showed an abnormal face and small prominent ears. No microcephaly or tracheoesophageal fistula was reported.

Family 2

Patient 3 was referred to the National Birth Defects Center at age 10 months because of microcephaly, tracheoesophageal fistula, hand abnormalities, and developmental delay.

Mother's pregnancy was normal with no history of exposures to teratogens. Delivery was at 40 weeks of gestation by caesarian section because of a prior section. At birth a tracheoesophageal fistula was noted and repaired. Following surgery she had a seizure that was treated with phenobarbital and Dilantin. At 9 months her motor function was at a 5–6-month level.

When examined at age 10 months, her length was 66 cm (50th centile for 5 ½ month's). Weight was 6.5 kg (50th centile for 5 months). OFC was 40 cm, (50th centile for 3 months). She had a broad nasal bridge but no epicanthal folds. Mouth appeared normal. Hands showed a single flexion crease of the 5th fingers, a small middle phalanx of the 4th finger with clinodactyly, hypoplasia of the middle phalanx of the 2nd finger with ulnar deviation, and symphalangism of both thumbs. There was dysplasia of the 5th toe nails.

Patient was lost to follow-up until age 13. At that time she was attending special education classes. Her reading was at the second grade level. Chromosomes were normal.

Both parents were adopted and their family history is unknown. Neither the parents nor a sister had any birth defects.

Family 3

Patient 4 was referred to the Division of Genetics/Dysmorphology at the University of Kentucky Chandler Medical Center for evaluation of multiple birth defects, including microcephaly, hand abnormalities, and tracheoesophageal fistula with esophageal atresia.

Pregnancy was normal except for decreased fetal movement. After a 35-week gestation, the baby was delivered vaginally and her Apgar scores were 2 after 1 minute and 9 after 5 minutes. Birth weight was 2,120 g (25th centile), length 44 cm (25th centile), and OFC 28 cm (2nd centile). Noted at birth were: tracheoesophageal fistula, esophageal atresia, patent ductus arteriosus, microcephaly, micrognathia, extra flexion creases on the middle phalanx of the third and fourth fingers, hyperextensible left thumb, and minor variations of the palmar flexion creases. She had epicanthal folds, short palpebral fissures, prominent tip of the nose, and slight posterior angulation of the ears. Chromosomes were normal.

Her mother (Patient 5) was also born with a tracheoesophageal fistula and esophageal atresia. She was judged to have normal intelligence but did have a learning disability. Head circumference was below the 2nd centile (50th centile for a 2-year-old). She had prominent eyes, upslanting palpebral fissures, flat nose, anteverted nostrils, and a high palate. Her hands showed transverse creases on the second and fourth interdigital areas, lack of flexion creases of the right thumb, and minor variations of the palmar flexion creases.

The proposita had a younger sister (Patient 6) with microcephaly and short fifth fingers with a single flexion crease. She had a normal CT scan of the head. A maternal brother had a cleft lip and palate and mild retardation. Another maternal sister (Patient 7) had short fifth fingers, microcephaly, and mild retardation, as did her daughter (Patient 8). The mother's mother was considered to be "slow" as was her brother, who also had a cleft lip and palate. There was also a history of mild retardation in four other relatives who were not examined.

Family 4

Patient 9, a 5-month-old girl, was first seen at the Division of Genetics/Dysmorphology at the University

Fig. 2. Face of mother 1 showing triangular shape, upslanting palpebral fissures, prominent lips, micrognathia, and asymmetry.

of Kentucky Chandler Medical Center for evaluation of multiple congenital anomalies. She was the product of a 35-week gestation complicated by polyhydramnios. Development was normal. Birth weight was 2,190 g (50th centile), length 46 cm (50th centile), and OFC 30 cm (2nd centile). A tracheoesophageal fistula and esophageal atresia noted at birth were repaired surgically. Also present at birth were microcephaly, a small anterior fontanel, narrow bifrontal diameter, small mouth, micrognathia, short fifth fingers, and hypoplastic distal flexion creases of the fourth fingers.

The patient's mother (Patient 10) was also born with a tracheoesophageal fistula and esophageal atresia. Head circumference was below the 2nd centile, the 50th centile for a 2-year-old. Her forehead was short and posteriorly recessed (Fig. 3). Nasal tip was full. Fifth fingers were short with hypoplastic distal flexion creases. Mother was considered mildly mentally retarded (she completed the 6th grade).

The proposita was the only child of this mother. There was an unsubstantiated history of other maternal relatives having small heads as well as some with cleft lip and/or cleft palate.

Family 5

Patient 11 was identified through the Spanish Collaborative Study of Congenital Malformations. He was the product of a 39-week gestation to a gravida 3, para 3, 31-year-old mother and 33-year-old father who were in good health and were non-consanguineous. Pregnancy and delivery were normal. At birth the baby weighed 1,840 g and his OFC was 26.5 cm, (3rd cen-

Fig. 3. Face and hands of mother of patient 9 showing microcephaly, short forehead, full nasal tip, and short 5th finger with hypoplastic distal flexion creases.

tile). A tracheoesophageal fistula and esophageal atresia were noted at birth. The infant died at 48 hours; no autopsy was performed. Chromosomes were normal.

The mother's first child, a girl, was normal. Her second one, also a girl, had an encephalocele and no other reported congenital anomalies. It was not known if the parents had any manifestations of this condition.

Family 6

Patient 12 was identified through the Spanish Collaborative Study of Congenital Malformations. He was the second son born to a gravida 2, para 2, 29-year-old woman and a nonconsanguineous 32-year-old man. During the 4th month of pregnancy, the mother was diagnosed as having toxoplasmosis and was treated with Spiramycin. The pregnancy was otherwise normal. After 38 weeks of gestation, the baby was born weighing 2,900 g. OFC was 31 cm (3rd centile). Also noted at birth were esophageal atresia, missing middle phalanx of the second and fifth fingers, and syndactyly between the second and third toes. Chromosome analysis was not done.

DISCUSSION

As more patients are being reported with this syndrome, we are now better able to define it. Table I lists the major findings of the syndrome. There is a significant amount of intrafamilial variability especially as it relates to the gastrointestinal findings. The original patients described by Feingold were very young when they were first reported and did not at that time exhibit any developmental delay, but they subsequently developed learning problems and attended special classes. Of our eight patients who were old enough to be properly evaluated, seven were mildly retarded or had learning difficulties in contrast to 52% of all of the reported cases. However, many of the reported patients did not have any formal intellectual testing and, therefore, it is likely that even a higher percentage of patients may have some cognitive problems.

Hand abnormalities are the most consistent physical finding of this syndrome being present in all of the patients. A common hand finding is shortness of the second and/or fifth fingers with clinodactyly and hypoplasia of the middle phalanx (Fig. 4). Syndactyly of the toes, usually toes 2 and 3, or 4 and 5, occurs frequently.

TABLE I. Major Clinical Findings

	Present report	All reports
Sex	F-9 (75%); M-3 (25%)	F-22 (63%); M-13 (37%)
	n %	n %
Hand abnormalities	11/11 (100)	32/32 (100)
Microcephaly	12/12 (100)	28/32 (87.5)
Foot abnormalities	4/5 (80)	23/26 (90)
TEF/EA/DA[a]	9/12 (75)	19/35 (54)
MR/LP[b]	7/8 (87)	14/27 (52)

[a]Tracheoesphageal fistula/esophageal atresia/duodenal atresia.
[b]Mental retardation/learning problems.

Fig. 4. Typical hand findings in patients with this syndrome with short 2nd and 5th fingers and clinodactyly and hypoplasia of the middle phalanx.

Microcephaly is also a common finding and most likely is the cause of the developmental delay. Gastrointestinal anomalies are not as consistent but are the most acute because they require immediate surgery and are present in slightly more than 50% of the patients. Tracheoesophageal fistula is the most common gastrointestinal anomaly, and it is usually associated with esophageal or duodenal atresia.

The face is frequently abnormal and consists of narrow and short palpebral fissures, micrognathia, anteverted nostrils, broad nasal bridge, prominent occiput, and ear anomalies.

Inheritance is autosomal dominant. In Feingold's first family, male-to-male transmission was present, and in 8 of the 11 reported families, there is transmission through at least two generations. Brunner and Winter [1991] noted that all of the findings present in these patients are also found in patients with deletions of chromosome 13 distal to band 13q14. They raised the possibility of chromosome 13 being a potential candidate for the mutation that is responsible for this syndrome. However, until a specific marker is found, the diagnosis remains a clinical one.

König et al. [1990] have proposed to name this syndrome the MMT syndrome because of the microcephaly, mesobrachyphalangy, and tracheoesophageal fistula. McKusick [1994] named it the oculodigitoesophagoduodenal syndrome. Hall [1994] has suggested the name tracheoesophageal fistula-esophageal atresia, multiple congenital anomaly syndrome: Feingold type. The incidence of this syndrome is not known, but if the number of recent reports of patients with this condition is any indication, it is not uncommon.

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